IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	**MDL No. 2:14-mn-02502-RMG**
	)	**This document relates to:**
	)	*All actions*

PFIZER'S SUR-REPLY TO PLAINTIFFS' REPLY
SUPPLEMENTAL DOSE BRIEF ON GENERAL CAUSATION [1395]

Pursuant to this Court's text order [1411], Pfizer respectfully submits this sur-reply to Plaintiffs' supplemental reply brief [1395].

I. Attorney Argument Does Not Satisfy This Court's Directive

Plaintiffs' reply confirms that they have not met their burden to offer reliable expert causation testimony on dose. This Court instructed that it is the experts, not counsel, who must opine on and reliably apply their expertise to the data. 10/22/15 Hr'g Tr. [1206] at 25:10-22. Plaintiffs' reply advances abundant lawyer argument and discusses documents not addressed by their experts in their dose reports.

Plaintiffs' characterizations of the data are frequently misguided, and contrary to this Court's instruction, because they are inconsistent with their experts' statements. Plaintiffs' experts admit that randomized clinical trials are necessary to show causation. *See* Quon Tr. [972-2] at 178:23-179:7; Gale Tr. [972-1] at 219:4-221:1. They admit that observational studies are subject to confounding and other limitations and cannot show causation. [redacted] Gale Tr. at 219:4-221:1, 223:5-16; Roberts, *The Truth About Statins* (2012) [1383-21] at 106; Quon Tr. at 296:16-297:2. [redacted]

[redacted] Plaintiffs attempt to overcome these admissions through lawyer opinions about, among other things, NDA glucose data, emails, regulatory documents, meta-analyses that do not address dose, and observational studies. Pls. Supp. Reply [1395] at 5-8, 11-13, 15-21. But Plaintiffs cannot expand or amend the expert record through lawyer argument. Plaintiffs' contention that certain data ***not*** relied on by their experts for their dose opinions "further support Plaintiffs' experts' opinions," *id.* at 16, is similarly misplaced.

Nor can lawyer opinion about the data cure the deficiencies in Plaintiffs' experts' opinions on dose and conjure a so-called "battle of the experts." *Id.* at 3, 27. "Without competent evidence on both sides, there can be no 'battle of the experts' in which a fact-finder could weigh competing claims." *In re Baycol Prods. Litig.*, 596 F. 3d 884, 892 (8th Cir. 2010). "The court's inquiry should not stop merely because plaintiffs attempt to characterize the situation as a 'battle of the experts.' There need be no battle, and no trial, if the court concludes that the admissible opinions of plaintiffs' experts would not allow a reasonable jury to find for plaintiffs on the issue of medical causation." *Carroll v. Litton Sys., Inc.*, 1990 WL 312969, at *42 (W.D.N.C. 1990) (emphasis omitted), *rev'd in part on other grounds*, 47 F.3d 1164 (4th Cir. 1995). This Court must determine whether Plaintiffs' experts' testimony "is based on sufficient facts and data" and whether they have "reliably applied [reliable] principles and methods to the facts of the case." Fed. R. Evid. 702; *see* Defs. Supp. Reply [1393] at 3-5. Because Plaintiffs' experts have not provided reliable, dose-specific evidence of an association between Lipitor and new diagnoses of diabetes, there is no causation, and thus no "battle of the experts."

II. Plaintiffs' "Weight of the Evidence" Argument Fails Under Rule 702

Plaintiffs' experts have not come forward with reliable evidence of a causal relationship between Lipitor and diabetes at any dose. They have not cited a single study reporting a statistically significant association at 10 mg. At 20 and 40 mg, they identified a single observational study (Cederberg) reporting a statstically significant association. As discussed in

Pfizer's opening brief, Cederberg has significant limitations and does not provide specific estimates at 20 mg or 40 mg. [redacted]

To this end, in their dose brief, Plaintiffs admitted, among other things, that the "data specific to the 20 mg and 40 mg doses" are "sparse" and "standing alone, … may have been insufficient" to show an increased risk. Pls. Supp. Br. [1384] at 8. They also asserted that an association at 10 mg "may be harder to detect or occur less frequently" than at 80 mg. *Id.* at 2.

In their reply brief, Plaintiffs disregard their prior dose-specific admissions. Instead, they argue that Pfizer has improperly attempted to "divide and conquer each individual piece of evidence relied upon by Plaintiffs' experts," and they further claim that "the totality of the evidence" reliably shows causation. Pls. Supp. Reply [1395] at 4. Yet the totality of the evidence, including its many limitations, does not demonstrate causation at any dose. Reliable methodology requires experts to evaluate "the internal validity of a study," by "account[ing] for the roles of bias, confounding factors, and the likelihood that the observed association is due to chance." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 604 (D.N.J. 2002), *aff'd*, 68 F. App'x 356 (3d Cir. 2003). Though Plaintiffs characterize the observational and glucose data as individual feathers, or pieces of a puzzle, that combine to show causation, their experts' testimony tells a different story. *See* Defs. Supp. Br. [1383] at 13-34. For instance, Dr. Quon admits that "observational studies are among the weakest type of evidence," Quon Tr. [972-2] at 286:21-23, and Dr. Gale admits that observational studies are hypothesis generating only and, thus, can only ask a question about a potential association to be answered by clinical trials. Gale Tr. [972-1] at 219:4-221:1, 223:5-16. [redacted] *Reference Manual on Scientific Evidence* 598-600 (3d ed. 2011) ("*RM (3d)*"). Neither source of evidence is thus capable of reliably showing whether

a true association, let alone causation, exists.

Plaintiffs thus advance a generalized contention that the "weight of the evidence" allows their experts to opine that Lipitor causes diabetes ***across the dose range***, rather than at specific doses. *See* Pls. Supp. Reply [1395] at 4. This position ignores the Court's order requiring a dose-specific causation analysis and is incapable of satisfying Rule 702. CMO 49 [1197] at 11. To this end, Plaintiffs recite a portion of *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11 (1st Cir. 2011), in which an expert used a so-called "weight of the evidence" methodology. *Id.* at 23. But as the *Milward* court made clear, "'[t]rial judges may evalute the data offered to support an expert's bottom-line opinions to determine if that data provides adequate support to mark the expert's testimony as reliable.'" *Id.* at 15 (citation omitted).

Notably, in *General Electric Co. v. Joiner*, the Supreme Court rejected the notion that employing a "weight of the evidence" methodology allows experts to avoid the limitations presented by individual studies. 522 U.S. 136, 146 (1997). In *Joiner*, the district court "examined the studies one by one and concluded that none was sufficient" to show general causation, but the Eleventh Circuit reversed, "expressly decid[ing] that a 'weight of the evidence' methodology was scientifically acceptable." *Joiner*, 522 U.S. at 153 (Stevens, J., concurring in part and dissenting in part). The Supreme Court then reversed the Eleventh Circuit, holding that "it was within the District Court's discretion to conclude that the studies upon which the experts relied were not sufficient, whether individually or in combination," to show general causation. *Id.* at 140-41, 146-47 (opinion of the Court).

Because the data here suffer from multiple limitations and do not support Plaintiffs' experts' opinions regarding causation, the Court is "left with nothing but the *ipse dixit* of the expert," *Sparling v. Doyle*, 2016 WL 236266, at *6 (W.D. Tex. 2016), which is inadmissible. *Joiner*, 522 U.S. at 146. It is "inconsistent with *Daubert*" for an expert to piece together inadequate categories of evidence, under the rubric of the totality of evidence, to form "a reliable theory." *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1216 n.21 (10th Cir. 2002). To do so amounts to nothing more than "a hollow whole of hollow parts." *Caraker v. Sandoz*

Pharms. Corp., 188 F. Supp. 2d 1026, 1040 (S.D. Ill. 2001).

"Weight of the evidence" is not a mantra that lawyers can chant in order to disguise the fact that what their experts offer is, in reality, nothing "more than subjective belief or unsupported speculation," *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590 (1993), which they interpret at will. Such a subjective approach is not grounded in the principles of science, but is ultimately driven by a preconceived, result-oriented belief system. As courts have recognized in excluding an expert's invocation of the "weight of evidence," such a methodology "is subjective – in the words of [plaintiff's] own expert – as opposed to scientific." *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 459 (W.D. Pa. 2003); *accord In re Denture Cream Prods. Liab. Litig.*, 2015 WL 392021, at *2, *34 (S.D. Fla. 2015). "[T]he 'weight-of-the-evidence' methodology" cannot be used as "a mere conclusion-oriented selection process that weighs more heavily those studies that supported an outcome." *Magistrini*, 180 F. Supp. 2d at 607. "Weight of the evidence" is a method used by "[r]egulatory and advisory bodies" and "results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances" where "[t]he agencies' threshold of proof is reasonably lower than that appropriate in tort law." *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996). It is thus not "scientifically acceptable for demonstrating a medical link" between an exposure and disease. *Id.*

In any event, among Plaintiffs' experts, only Dr. Singh addresses any weighting of evidence, but he does so in a subjective and qualitative fashion, rather than on a quantitative basis. For instance, Dr. Singh "down weighted" the glucose data, states that all of the observational studies together cannot show causation, and admits that the gold standard clinical trial data at 10 mg do not report a statistically significant association. Singh Supp. Rpt. [1383-1] at 2; [redacted] An "analytical gap" thus exists between whatever weighting Dr. Singh ascribes and his bottom-line opinion. *Joiner*, 522 U.S. at 146. Though Dr. Singh ultimately opines that Lipitor 10 mg causes diabetes, that opinion cannot reliably follow from the premises of any weighting, and much less so can

Plaintiffs justify any derivative opinions at 20 mg and 40 mg. [redacted]

[redacted]

[redacted]

III. Plaintiffs Have Not Identified a Reliable Methodology

Plaintiffs claim that "the methodology used" by their experts "is precisely the same as the methodology used by Defendants' experts: consideration and analysis of the published papers and studies." Pls. Supp. Reply [1395] at 24. But "consideration and analysis" of published papers – as a generalized abstract proposition – is not a methodology, let alone an objective, testable, or reliable one. By "adopting an excessive level of generality in [the] gatekeeping inquiry," Plaintiffs should not be permitted to invite this Court's *Daubert* analysis to have "fatally erred by applying criteria at a standard of meaninglessly high generality rather than boring in on the precise state of scientific knowledge in this case." *Black v. Food Lion, Inc.*, 171 F.3d 308, 313-14 (5th Cir. 1999). "Review of the studies" is just another subjective "'weight of the evidence' analysis," and such "methods of proving general causation are insufficient," "have the potential to mislead a jury," and are inadmissible. *Denture Cream*, 2015 WL 392021, at *2, *34.

In an attempt to support their so-called "reviewing studies" methodology, Plaintiffs quote the Reference Manual for the proposition that "deciding whether associations are causal typically is not a matter of statistics alone, but also rests on scientific judgment." Pls. Supp. Reply [1395] at 22 (quoting *RM (3d)* at 222). "'Judgment,'" of course, "does not substitute for scientific method; without a reliable method, result-oriented 'judgment' cannot be distinguished from scientifically or methodologically-based judgment." *Magistrini*, 180 F. Supp. 2d at 607. Plaintiffs' experts have identified no such scientific method here.

Critically, to make a judgment about whether an association is causal, there must first be a ***true*** association that adequately accounts for chance, bias, and confounding. As the Reference Manual states, it is "only ***after***" a true association has been established – after "researchers first look for alternative explanations for the association, such as bias or confounding" or chance –

that the Bradford Hill factors are applied to assess whether a causal relationship exists. *RM (3d)* at 598-99. Because Plaintiffs' experts cannot overcome the recognized problems of chance, bias, and confounding in the data they cite, there is no true association between Lipitor and new diagnoses of diabetes and, thus, they cannot properly establish any causal relationship.

Plaintiffs argue that their "experts were specifically precluded by the Court … from considering the totality of the evidence." Pls. Supp. Reply [1395] at 25 (citing CMO 49). To the contrary, this Court ***granted*** Plaintiffs' specific request that, in addition to the materials cited in Plaintiffs' September 29, 2015 submission, their experts be permitted to rely on studies cited in prior reports. 10/22/15 Hr'g Tr. [1206] at 54:21-55:16; CMO 49 [1197] at 12. Moreover, this Court stated that "[f]or each dosage level on which the expert opines, the report must ***set forth the facts and data*** that form the basis for the experts' opinion(s) that Lipitor causes diabetes at particular dosages ***and describe the methodology*** used to reach her opinion(s)." CMO 49 at 11 (emphasis added). This Court found that Plaintiffs' experts' original opinions were unreliable because they did not address causation by dose, but granted them the opportunity to do so by supplementing their expert opinions, allowing them even to cite additional materials Plaintiffs identified as relating to causation by dose. Plaintiffs' experts had a full and fair opportunity to proffer reliable opinions.

Further, in purporting to apply their "review studies" methodology, Plaintiffs cite inapposite materials that cannot meet their burden to show a dose-specific association between Lipitor and new diagnoses of diabetes. Plaintiffs cite six meta-analyses that they say support their opinions that Lipitor causes diabetes, Pls. Supp. Reply [1395] at 16-17, but ***none*** calculates a summary (or pooled) odds ratio of any dose of Lipitor – and only one was addressed in their experts' dose reports.[1] They also cite Gastaldi,[2] an editorial, in contravention of CMO 49, and Goldstein,[3] which do not address any dose of Lipitor. *See* Defs. Supp. Reply [1393] at 4-5.

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[1] Preiss et al., *Risk of incident diabetes with intensive-dose compared with moderate dose statin therapy: a meta-analysis*, 305 JAMA 2556 (2011).

[2] Gastaldi & Philippe, *Statins and diabetes: The plot thickens*, 30 J. Gen. Int. Med. 1572 (2015).

[3] Goldstein & Mascitelli, *Do statins cause diabetes?*, 13 Curr. Diab. Rep. 381 (2013).

Plaintiffs also cite portions of Pfizer's 2010 response to the United Kingdom's regulatory authority, yet none of their experts relied on any of those passages in their dose reports. Pls. Supp. Reply at 16 n.2. Nor do those passages address any dose-specific association.

Finally, Plaintiffs mischaracterize Pfizer's points about the observational studies cited by some or all of Plaintiffs' experts. For example, Plaintiffs contend that "Pfizer's only criticism" of the Chen study is that it "did not adjust for *every* variable that Pfizer could imagine," and that its "only true criticism of the Culver paper is … that it did not adjust for *every conceivable* variable." Pls. Supp. Reply [1395] at 20-21. These characterizations are untrue and a caricature of the analyses by Pfizer's experts – and of various admissions by Plaintiffs' experts – which showed that Chen and Culver do not report dose-specific results for Lipitor, failed to adjust for many key confounding variables, and suffered from other notable limitations. Defs. Supp. Br. [1383] at 20-22. As Dr. Singh testified, [redacted]

CONCLUSION

For the foregoing reasons and those set forth in Pfizer's prior briefing and at the hearing, Pfizer's motion to exclude Plaintiffs' general causation evidence should be granted.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that, this 4th day of March, 2016, I have electronically filed a copy of the above and foregoing with Clerk of the Court using the ECF system, which sent notification of such filing to counsel of record.

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